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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SRIVASTAVA, KAILASH C	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/669,051	FRANANO, NICOLAS F.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *27.08.2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Request for continued examination (i.e., RCE) under 37 CFR §1.114, including the fee set forth in 37 CFR §1.17(e), was filed in this application on 27 August, 2004 after a Final action mailed 27 February 2004. Since this application is eligible for continued examination under 37 CFR §1.114, and the fee set forth in 37 CFR §1.17(e) has been timely paid, the finality of the previous Office action mailed 27 February 2004 has been withdrawn pursuant to 37 CFR §1.114. Applicants' submission filed on 27 August 2004 has been entered. Accordingly an RCE has been established and the action on RCE follows.

2. Applicant's responsive Amendment filed 27 August 2004 is acknowledged and entered. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

3. In view of the resubmissions, amendments and remarks presented in Applicant's response filed 27 August 20004, objections to the Supplemental Information disclosure and Claims 59-60 in the Office action mailed 27 February 2004 are herby withdrawn.

4. In view of the amendments and arguments presented in Applicant's response filed 27 August 20004, the rejection of Claims 56-57 under 35 U.S.C. § 102 (b) as anticipated by Anidjar et al. (Annals of Vascular Surgery, 1994, Volume 8, Pages 1128-1136) and Ooyama et al. (Ciba Foundation Symposium, 1995, Volume 1992, Pages 307-320) in the Office action mailed 27 February 2004) is hereby withdrawn.

5. In view of the amendments and arguments presented in Applicant's response filed 27 August 20004, the rejection of Claims 56-68 under 35 U.S.C. § 103 (a) **in** the Office action mailed 27 February 2004 over Anidjar et al. (Annals of Vascular Surgery, 1994, Volume 8, Pages 1128-1136) and Ooyama et al. (Ciba Foundation Symposium, 1995, Volume 1992, Pages 307-320) in view of Strindberg et al. (Journal of Investigative Surgery, 1998, Volume 11, Pages 185-198) in the Office action mailed 27 February 2004 is hereby withdrawn.

CLAIMS STATUS

6. Claim 69 has been added.

7. Claims 56-68 have been amended.

8. Claims 56-69 are pending and are examined on Merits.

Information Disclosure Statement

9. Applicant's Information Disclosure (i.e., IDS) filed 27 August 2004 has been made of record and considered.

Objection To Specification

10. 35 U.S.C. §112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is objected to because certain technical names are misspelled (e.g., "proteosytic" at Page 7, Line 22; *Clostridia histolyticum* at Page 12, Line 6), repeated usage of some phrases at the beginning and again at the end of same sentence (e.g., Page 3, Lines 19-21; Page 9, Lines 5-8; Page 11, Lines 21-22 and 26) or certain statements (e.g., Page 5, Line 24 and 26-27) make several portions of the specification unclear. Appropriate correction is required. Applicant is cautioned to ensure that no new matter is added while corrections are made to alleviate above-identified minor errors to the specification.

Examiner has not thoroughly checked the entire specification to determine the presence of all possible minor errors. Applicant 's cooperation is requested in correcting any errors in the specification of which applicants may become aware. Applicants are warned to exercise caution that no new matter is added while revising the specification for said corrections.

11. In view of applicant's amendment filed 27 August 2004, following are new rejections to claims;

i. 56-69 under 35 U.S.C. §112 first and second paragraphs;
ii. 56, 59-63 and 67-68 under 35 U.S.C. §102(b);
iii. 56-63, 65 and 67-68 under 35 U.S.C. §102(a); and
iv. 56-69 under 35 U.S.C. §103(a).

Claims Rejections Under 35 U.S.C § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. § 112 that form the basis for the rejections under this section made in this Office action:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

13. Claims 56-69 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are

directed to a method comprising local administration to the wall of an artery or vein in a human subject a composition comprising collagenase or an elastase to treat an artery or vein in a human subject, wherein the artery or vein is obstructed. Said administration "results in proteolysis of elastin in the wall of the artery or vein leading to enlargement of the diameter of the artery or vein". The method further comprises administering said composition by a catheter, said obstruction being stenosis, coronary obstruction, "intimal hyperplasia" or the artery or vein is connected to an "arteriovenous hemodialysis graft". Claims are also directed to administration of said composition to "an isolated or selected segment of the artery or vein located within the human subject".

From the record of the presently filed written disclosure, the specification enables with working examples treatment via administration of a collagenase preparation through catheter in a dog (i.e., an experimental animal):

- strictures in the "common bile duct" (See Examples 4 and 5 at Specification page 19, Line 16 to Page 22, Line 22); and
- "stenosis due to intimal hyperplasia between the femoral artery and the femoral vein" (Example 6 at Specification page 22, Line 23 to Page 23, Line 22).

However, the specification as presented does not reasonably provide evidence of the claimed method with working examples to treat in a human patient via in-vivo administration of an elastase preparation:

- obstructed arteries or veins/ stenosis/ intimal hyperplasia.

In absence of any working example, the discussion presented at different places in the specification (e.g., page 6, Lines 11-16; Page 7, Lines 19-22; Page 12, Lines 3-4) seems to be mere contemplation or conjecture to treat intimal hyperplasia or obstruction of arteries, veins or bile duct with in-vivo administration of a preparation comprising elastase, or elastase mixed with collagenase. Furthermore, Example 7 as presented is merely a discussion of a planned experiment to be performed at some time in future. Also, applicant admits on record that in certain embodiments, to preserve the elastic properties of the conduit, degradation of elastin is not desired and "therapeutic agents comprising only enzymes, such as collagenase, that do not degrade elastin can be employed.

A person of skill would not be able to practice the invention because undue experimentation will be required to obtain a method to treat intimal hyperplasia or obstruction of arteries, veins or bile duct with in-vivo administration of a preparation comprising elastase, or elastase mixed with collagenase in a human patient cited *supra*. The person of skill will not be able to practice the claimed invention cited *supra* due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level

of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Undue experimentation will be necessary because there is no recited guidance, i.e., all the steps to obtain the instantly claimed method "via in-vivo" administering a composition comprising elastase have not been recited in the claimed invention.

14. Claims 56-69 are rejected under 35 U.S.C. § 112, first paragraph, because the claimed composition does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

From the record of the present written disclosure, the scope of the claimed invention recited in claims 56-69 is not supported by the specification on record because in said specification there are a number of examples (Examples 4-6) showing treatment via administration of a collagenase preparation through catheter of strictures in the "common bile duct" of dogs (e.g., Specification page 19, Line 16 to Page 22, Line 22) and "stenosis due to intimal hyperplasia between the femoral artery and the femoral vein" of dogs (Example 6 at Specification page 22, Line 23 to Page 23, Line 22). . However, said specification does not show an example demonstrating treating obstructed arteries or veins/ stenosis/ intimal hyperplasia in a human patient or in an experimental model (e.g., dog) via in-vivo administration of an elastase preparation.

Based on the description provided in the specification, a person of ordinary skill would not be able to practice the invention because undue experimentation will be required to practice the invention cited *supra.* Undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary to delineate all the steps to obtain a treatment method comprising administration of an elastase preparation to the wall of an artery or vein, or bile duct to treat blockage or stenosis/ intimal hyperplasia; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

15. Claims 56-69 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In Claim 56, one or more essential steps necessary to carry out the claimed invention is entirely missing. It is not clear how one of skill can determine why the artery or vein is being treated according to Claim 1, without a mention of particular condition in/of the artery or vein. Accordingly, one or more essential steps necessary to successfully carry out the claimed invention is clearly missing from the claim language (See MPEP§2172.01). It is strongly suggested that

independent claim 56 be expanded upon so as to recite a complete, fully defined method, using the instant specification as a guide (e.g., Page 1, Lines 15,19).

- The recitation "susceptible to" renders Claim 66 indefinite because this term in and by itself denotes a futuristic event. The metes and bounds of the claimed subject matter are not clearly defined. The examiner suggests that the applicants define the metes and bounds of the term "susceptible to".

All other claims depend directly/indirectly from the rejected claims (e.g., Claim 83) and are, therefore, also rejected under 35 U.S.C. §112, second paragraph for the reasons set forth above.

Claims Rejections Under 35 U.S.C § 102

16. Amended Claims 56, 59-63 and 67-68 are rejected under 35 U.S.C. §102 (b) as anticipated by Wolinsky (U.S. Patent 4,636,195).

Claims recite a method comprising local administration to the wall of an artery or vein in a human subject a composition comprising collagenase to treat an artery or vein in a human subject, wherein the artery or vein is obstructed. Said administration "results in proteolysis of elastin in the wall of the artery or vein leading to enlargement of the diameter of the artery or vein". The method further comprises administering said composition by a catheter, said obstruction being stenosis or coronary obstruction. Claims are also directed to administering said composition to "an isolated or selected segment of the artery or vein located within the human subject".

Wolinsky discloses a method to relieve an arterial obstruction via inserting a catheter into an artery, wherein said catheter is expansible to the arterial diameter against the arterial wall for delivering a solution to solubilize plaque (Column 6, Lines 18-25), said solubilizing solution comprising collagenase at about 20μg/cc to 400 μg/cc of solubilizing solution (Column 6, Lines 47-49). Said obstruction being a stenosis (Column 2, Lines 18-20) of coronary arteries (Column 1, Lines 12-14). Since Wolinsky discusses composition of human arterial plaques causing clinical problems (Column 1, Line64 to Column 2, Line 10) and delivering a composition comprising collagenase via a catheter such that the catheter is expansable to the arterial diameter against the arterial wall to relieve arterial stenosis; inherently, Wolinsky discloses a method to alleviate arterial obstruction in a human patient via injecting into the arterial wall a collagenase composition through a catheter. Also, since said plaque is only in a portion of said artery, said artery being a coronary artery; Wolinsky inherently teaches administering a collagenase composition to a selected, isolated portion of the artery in a human patient. Furthermore, administration of some quantity of collagenase composition according to Wolinsky's method upon its administration would

inherently function in the same way as claimed instantly because, same composition is being administered through same apparatus and is alleviating the same problem (i.e., arterial blockage or stenosis) as is recited in the claimed invention. Therefore, the prior art method inherently must function as instantly claimed (See e.g., In re Best, 195 USPQ 430, 433-CCPA 1977).

Therefore, the reference is deemed to anticipate the cited claims.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.***

18. Amended Claims 56-63, 65 and 67-68 are rejected under 35 U.S.C. §102 (a) as anticipated by Dev et al (U.S. Patent 5, 944,710).

Claims recite a method comprising local administration to the wall of an artery or vein in a human subject a composition comprising collagenase/ elastase to treat an artery or vein in a human subject, wherein the artery or vein is obstructed. Said administration "results in proteolysis of elastin in the wall of the artery or vein leading to enlargement of the diameter of the artery or vein". The method further comprises administering said composition by a catheter, said obstruction being stenosis or coronary obstruction. Claims are also directed to administering said composition to "an isolated or selected segment of the artery or vein located within the human subject".

Dev et al. disclose a method to unblock clogged arteries and cardiovascular restenosis via local intravascular delivery through a catheter to the endothelial lining of a blood vessel into a subject (Column 1, Lines 14-44; Column 6, Lines 18-25 and 46-50; Column 16, Lines 42-51) an antirestonotic composition comprising collagenase/ elastase (Column 5, Lines 9-10). Since Dev et al. teach delivering a composition comprising collagenase/elastase via a catheter to the endothelial lining of a blood vessel; inherently, Dev et al., disclose a method to alleviate arterial obstruction in a human patient via injecting into the vascular wall a collagenase/elastase composition through a catheter. Also, since said composition is delivered only to a portion of said blood vessel, Dev et al., inherently teach administering a collagenase//elastase composition to a selected, isolated portion of a blood vessel in a human patient. Furthermore, administration of some quantity of said composition comprising collagenase/elastase according to Dev et al's method would upon its administration, inherently function in the same way (i.e., proteolysis of elastin in the wall of artery or vein) as instantly claimed; because, same composition is being administered through same apparatus and is alleviating the same problem (i.e., blockage in a blood vessel or

cardiovascular restenosis) as is recited in the claimed invention. Therefore, the prior art method inherently must function as instantly claimed (See e.g., In re Best, 195 USPQ 430, 433-CCPA 1977) to alleviate blockage in a coronary artery and cardiovascular restenosis.

Therefore, the reference is deemed to anticipate the cited claims.

Claims Rejections Under 35 U.S.C §103(a)

19. Claims 56-69 are rejected under 35 U.S.C. §103(a) as obvious over Wolinsky (U.S. Patent 4,636,195) in view of Dev et al (U.S. Patent 5, 944,710).

Wolinsky's teachings have already been discussed *supra*. Wolinsky, however, does not teach administering a composition comprising elastase, nor explicitly teaches that said composition is administered to the wall of a blood vessel.

Dev et al. explicitly teach that a composition comprising elstase/collagenase is administered to the cells of endothelial lining of a blood vessel via a catheter. Note that the endothelial lining of the blood vessel comprises the wall of a blood vessel. Furthermore, a blood vessel encompasses both an artery or a vein and any artery or vein. Thus, Dev et al. teach de-clogging an obstructed artery or a vein via injecting to the wall of said artery or vein a composition comprising collagenase/elastase through a catheter and further teach applying said method for cardiologic applications (Column 3, Lines 34-45). Consequently, Dev et al. teach de-clogging vascular obstruction encompassing an artery or vein, stenosis, artery or vein connected to an arteriovenous hemodialysis graft, coronary obstruction or obstruction by intimal hyperplasia.

One having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Kolinsky according to teachings from Dev et al. to obtain a method to declogg an obstructed blood vessel, wherein said clogging is stenosis, artery or vein connected to an arteriovenous hemodialysis graft, coronary obstruction or obstruction by intimal hyperplasia via delivering to the blood vessel wall a composition comprising collagenase/ elastase through a catheter, because each of the prior art references teach de-clogging a blood vessel and Dev et al. beneficially teach that said composition comprising collagenase/elastse is delivered to vascular endothelial lining (i.e., vascular wall) and is applicable to cardiologic applications. Thus, Dev et al. remedy the deficiency of elastase and delivery to a vessel/ arterial/ venous wall a composition comprising elastase/collagenase in Wolinsky's teachings.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify/combine Wolinsky's. teachings with those from Dev et al. to obtain a

method to de-clogg an obstructed blood vessel, wherein said clogging is stenosis, artery or vein connected to an arteriovenous hemodialysis graft, coronary obstruction or obstruction by intimal hyperplasia via delivering to the blood vessel wall a composition comprising collagenase/ elastase through a catheter. Dev et al. remedy the deficiency of elastase and delivery to a vessel/ arterial/ venous wall a composition comprising elastase/collagenase in Wolinskky's teachings. Instantly claimed arteriovenous hemodialysis graft, or obstruction by intimal hyperplasia is not explicitly taught taught in the cited prior arts. However, since the prior art teaches application of prior art method to a cardiologic application. the adjustment of particular conventional working conditions (e.g., application of instantly claimed method to a particular type of blood vessel obstruction) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan.

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

CONCLUSION

20. No Claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 8:15 A.M. to 6:45 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (571) 272-0926 Monday through Thursday. The fax phone number for the organization where this application or proceeding is assigned is (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kailash C. Srivastava, Ph.D.
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November 16, 2004

RALPH GITOMER
PRIMARY EXAMINER
GROUP 1200